SYNTHESIS OF A 2,6-DITHIA-6b,8c-DIAZADICYCLOPENT[ef,kl]s-INDACENE AS A PENTACYCLIC 16π HETEROANNULENE OF BIS NITROGEN-BRIDGED TYPE

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Abstract —— As a new 16π heteroannulene with two nitrogen bridges, a 2,6-dithia-6b,8c-diazadicyclopent[ef,kl]s-indacene was synthesized through the repeated acetic anhydride cyclizations of 3,8-dimethyl-5,10-dihydrodithiazolo[3,4-a:3',4'-d]pyrazine-4,9-diium salts, the dimer of 4-halomethyl-2-methylthiazoles.

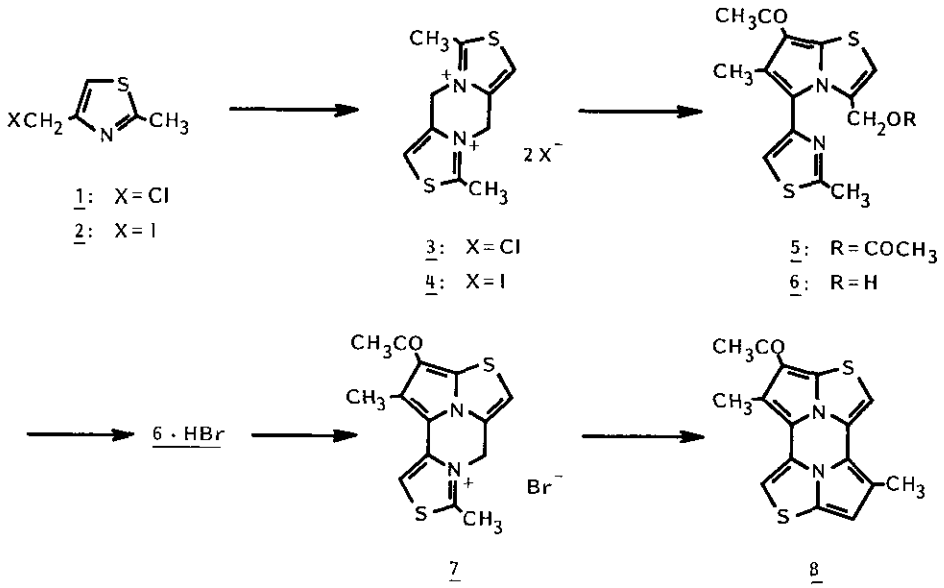
Although a great number of nitrogen-bridged annulenes involving tricyclic systems called cyclazine[1] have been synthesized so far, most of them are aromatic types with 4n+2 π-electrons on their perimeter. The families with 4n π-electrons are quite limited. Pyrido[2,1,6-ij]qunolizines[2] and 8b,8c-diazapyracyclenes[3] as typical examples of 12π nitrogen-bridged annulenes have attracted much attention of theoretical chemists.

Aiming at opening a new route toward nitrogen-bridged annulenes by the utilization of the quaternary salts of nitrogen heteroaromatics[4], we have investigated the cycloadditions of anhydro-3,4-dihydro-2H-pyrido[2,1-b][1,3]thiazin-3-on-5-ium hydroxide and synthesized 12π tricyclic annulenes, [1,3]thiazino[4,3,2-cd]indolizines[5].

The present communication describes the synthesis of a new 16π heteroannulene with two nitrogen bridges, a 2,6-dithia-6b,8c-diazadicyclopent[ef,kl]s-indacene, starting from 3,8-dimethyl-5,10-dihydrodithiazolo[3,4-a:3',4'-d]pyrazine-4,9-diium salts.

The starting compound, 4-chloromethyl-2-methylthiazole 1, is readily available in

high yield from thioacetamide and 1,3-dichloro-2-propanone[6]. The cyclodimerization of 1 was accomplished by heating. Although heating 1 at 110 °C without solvent led to a mixture of several water-soluble compounds, the cyclized dimer of 1, 3,8-dimethyl-5,10-dihydrodithiazolo[3,4-a:3',4'-d]pyrazine-4,9-diium dichloride 3, was obtained in 70% yield when 1 was heated in such a polar solvent as sulfolane (tetrahydrothiophene-1,1-dioxide) for 5 h. As the hygroscopic salt 3 was found to afford only poor yield of the cyclized product 5 in the following step of acetic anhydride cyclization, its counter anions were exchanged to iodides. Treatment of an aqueous solution of 3 with concentrated hydroiodic acid at room temperature precipitated the diiodide 4 in 77% yield. This water-insoluble salt 4, therefore easy to dry, was used for the following reactions. The diiodide 4 was accessible by another route: the chloromethylthiazole 1 was first converted into 4-iodomethyl-2-methylthiazole 2 in a quantitative yield by treating 1 with sodium iodide in diluted hydroiodic acid at 50 °C for 3 h, and then 2 was heated under reflux in methanol to give 43% of 4.



A mixture of 4, sodium acetate, and acetic anhydride was heated under reflux in N,N-dimethylformamide (DMF) for 3 h. Usual hydrolytic work-up and chromatographic separation (silica gel-chloroform) gave an unexpected product, 3-acetoxymethyl-7-

acetyl-6-methyl-5-(2-methyl-4-thiazolyl)pyrrolo[2,1-b]thiazole 5 (mp 174-175 °C), in 85% yield. The undesired pyrazine ring cleavage was caused by the attack of an acetoxy anion, and the acetylation was due to high reactivity at the 7-position of pyrrolo[2,1-b]thiazole ring toward a nucleophilic substitution. To avoid these two stages, various reaction conditions using all combinations of the acetylating reagents (acetic anhydride and acetyl chloride) and the bases (pyridine, triethylamine, and sodium acetate) were examined. However, 5 was the only product and the yields were less satisfactory. Therefore, the synthesis was continued using 5.

The ester 5 was readily converted into the alcohol 6 (mp 192-193 °C) through an ester exchange reaction. Thus, 5 was allowed to reflux in excess of methanol in the presence of a catalytic amount of concentrated sulfuric acid for 4 h to provide 6 in 78% yield.

For the recyclization into 7, halogenation of 6 was necessary. However, this step was rather trouble-making. The reaction of 6 with aqueous or gaseous hydrogen bromide in chloroform under reflux or at room temperature gave the hydrobromide of 6 and the same reaction in acetic acid produced the hydrobromide of 5. After some struggles, we found that the cyclization into 7 took place in 73% yield when 6·HBr was heated under nitrogen without solvent at 150-160 °C for 0.5 h.

The final acetic anhydride cyclization of 7 was successfully performed by heating the mixture of 7, each excess amounts of acetic anhydride and triethylamine at 140 °C for 5 min. Thus, orange crystals of 3-acetyl-4,8-dimethyl-2,6-dithia-6b,8c-diazadicyclopent[ef,kl]s-indacene 8 (mp 245-246 °C) were synthesized in 57% yield. The structural assignment of 8 was based upon the ^{1}H-NMR spectra as well as the elemental analysis (^{1}H-NMR in $CDCl_3$: δ2.24 (3H, s), 2.36 (3H, s), 2.40 (3H, s), 5.92 (1H, s), 6.04 (1H, s), and 6.12 ppm (1H, s). Anal. Found: C, 61.3; H, 4.1; N, 8.8%. Calcd for $C_{16}H_{12}ON_2S_2$: C, 61.5; H, 3.9; N, 9.0%.).

The ring hydrogens of 8 appeared only slightly upfield of those of 6-methylpyrrolo-[2,1-b]thiazole[7] (2-H: δ6.54, 3-H: 7.25, 5-H: 7.00, and 7-H: 6.08 ppm), indicating that both the pyrrolo[2,1-b]thiazole rings of 8 would not lie in the same plane. Thermal stability of 8 might not be inconsistent with the above spectral data. However, 8 showed rather different chemical properties. No introduction of an acetyl moiety in the final cyclization process indicates that the 7-position of 8 is no longer reactive toward acetylation. A high yield acetylation at the 7-

position of pyrrolo[2,1-b]thiazole ring was actually demonstrated in the first cyclization stage (from 4 to 5). In addition, the 3-acetyl moiety could not be removed when 8 was heated under reflux in chloroform, tetrahydrofuran, or DMF in the presence of hydrochloric acid, while these conditions are very effective for the elimination of acetyl group at the 5- or 7-position of pyrrolo[2,1-b]thiazole ring.

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